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Schizophrenia, Myelination, and Delayed Corollary Discharges: A Hypothesis

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Any etiological theory of schizophrenia must account for at least 3 distinctive features of the disorder, namely its excessive dopamine neurotransmission, its frequent periadolescent onset, and its bizarre, pathognomonic symptoms. In this article, we theorize that each of these features could arise from a single underlying cause—namely abnormal myelination of late-developing frontal white matter fasciculi. Specifically, we suggest that abnormalities in frontal myelination result in conduction delays in the efference copies initiated by willed actions. These conduction delays cause the resulting corollary discharges to be generated too late to suppress the sensory consequences of the willed actions. The resulting ambiguity as to the origins of these actions represents a phenomenologically and neurophysiologically significant prediction error. On a phenomenological level, the perception of salience in a self-generated action leads to confusion as to its origins and, consequently, passivity experiences and auditory hallucinations. On a neurophysiological level, this prediction error leads to the increased activity of dopaminergic neurons in the midbrain. This dopaminergic activity causes previously insignificant events to be perceived as salient, which exacerbates the budding hallucinations and passivity experiences and triggers additional first-rank symptoms such as delusions of reference. The article concludes with a discussion of the implications of the theory and some testable predictions which may form a worthwhile basis for future research.

Key words: white matter/dopamine/neurodevelopment/salience/self-monitoring/efference copy/myelin

Any etiological theory of schizophrenia must account for at least 3 common and distinctive features of the disorder. First, it must account for the excessive dopamine neurotransmission that has been associated with the psychotic symptoms of schizophrenia. Evidence for this hyperdopaminergia, which is consistent with increases in the phasic activity of midbrain dopaminergic neurons,[1] is provided by the fact that the vast majority of antipsychotic medications act as dopamine antagonists,[2] combined with the fact that the administration of dopamine agonists to healthy people has consistently been shown to give rise to schizophrenia-like psychotic symptoms.[3,4] Second, the theory must account for why the symptoms of schizophrenia so commonly first present in late adolescence and early adulthood, with the majority of cases occurring between the ages of 16 and 30 years.[5] Third, the theory must account for the mechanism that gives rise to such bizarre yet pathognomonic clinical symptoms as passivity experiences, auditory hallucinations, and delusions of reference. The purpose of this article is to offer a theory as to how these 3 distinctive features could all potentially arise from a single underlying cause—namely, abnormal myelination of the frontally projecting white matter fasciculi during periadolescent neurodevelopment. Specifically, we will argue that abnormalities in frontal myelination cause conduction delays in the efference copies that are involved in predicting the neural consequences of self-generated actions. These conduction delays lead to prediction errors which, in addition to causing certain psychotic symptoms directly, ultimately also underpin the excessive phasic dopamine neurotransmission that has been associated with the psychotic symptoms of schizophrenia.[6,7] The article will conclude with some testable predictions which may form a worthwhile basis for future research. The theory presented here has been heavily influenced by the ideas of several previous researchers, particularly Feinberg,[8] Frith,[9] Fletcher,[10] Kapur,[11] Andreasen,[12] and Bartzokis,[13] and we gratefully acknowledge their intellectual contributions.

After more than 2 decades of neuroimaging research, it is now well established that patients with schizophrenia exhibit structural abnormalities in the cerebral white matter. The white matter of the central nervous system is

primarily constituted of the phospholipid processes of a certain type of neuroglia known as oligodendrocytes. The compacted processes of these oligodendrocytes, known as myelin, ensheath the axons of nearby neurons. The myelin acts as electrical insulation for the ensheathed axon, which both helps to preserve the amplitude and increase the conduction velocity of the propagating axon potential.[14] Myelinated axons with similar destinations tend to bundle together into white matter fasciculi, which ultimately constitute the primary physical infrastructure for communication between spatially disparate populations of neurons. Given its role as the primary infrastructure for long-distance communication in the brain, it is perhaps not surprising that abnormalities in the white matter fasciculi have been implicated in schizophrenia, particularly by those "disconnectivity" theories (eg, Bartzokis,[13] Andreasen,[15] Fields,[16] and Walterfang et al[17]) that emphasize the role of abnormal interactions between brain regions, as opposed to abnormal brain regions per se, in the etiology of the disorder.[18] Evidence for these theories has come from an increasingly large number of studies that have observed white matter abnormalities in patients with schizophrenia, either "postmortem" with electron microscopy[19,20] or in vivo with structural MRI[21] or, more recently, diffusion-tensor imaging (see reviews in Whitford et al,[22] Kubicki et al[23], and Shenton and Kubicki[24]). While the location, extent, and timing of these abnormalities have not yet been definitively established, it appears that not all fasciculi are equally abnormal in patients with schizophrenia. Specifically, while the primary sensorimotor fasciculi appear to be comparatively unaffected in patients in schizophrenia, structural abnormalities have consistently been reported in the fasciculi connecting the frontal lobe with the rest of the brain, such as the uncinate fasciculus,[25,26] arcuate fasciculus,[27,28] superior longitudinal fasciculus,[29,30] and cingulum bundle.[31,32] Aside from their frontal origins—a feature that is especially notable in light of the growing evidence for frontotemporal[33,34] and frontoparietal[35,36] functional misconnectivities in patients with schizophrenia—these particular fasciculi have at least 2 points in common. First, damage to these frontal fasciculi has been associated with the development of first-rank psychotic symptoms, such as, eg, in patients with multiple sclerosis[37] and, more commonly, in patients with the demyelinating disorder metachromatic leukodystrophy, particularly when the disorder first presents in early adulthood.[38,39] Second, these frontal fasciculi are among the last fasciculi to structurally mature in the developing human brain, with myelination thought to continue through adolescence and into early adulthood,[40–43] which is a period that corresponds to the most common age-of-onset for schizophrenia. When combined with the fact that schizophrenia patients exhibit a range of myelin-specific abnormalities—including reduced numbers of oligodendrocytes,[19] irregular myelin microstructure,[20] and subnormal expression of myelin-related genes[44]—there is reason to believe that schizophrenia may be underpinned by irregularities in the normative processes of periadolescent myelination,[13] particularly in the late-developing frontal fasciculi.

If schizophrenia is ultimately underpinned by abnormalities in the normative processes of periadolescent myelination in the frontal fasciculi, then the question remains as to both "how" and "why" abnormalities in these fasciculi lead to the distinctive, diagnostic symptoms and excessive dopamine neurotransmission that are characteristic of the disorder. One possibility, which we explore in this article, relates to myelin's role in modulating the conduction velocity of action potentials.

It is well established that myelinated axons typically have higher conduction velocities than unmyelinated axons of the same caliber[45] and that damage to the myelin can result in conduction delays in neural discharges. For example, multiple sclerosis patients with damage to the myelin of the optic nerve typically exhibit conduction delays of around 20 ms in the latency of the P1 component of the visual-evoked potential.[46–48] Given the frontal white matter abnormalities exhibited by patients with schizophrenia, it seems reasonable to assume that they would also experience conduction delays in neural discharges traveling along these frontal fasciculi. In a general sense, such conduction delays might be expected to result in a temporal discoordination between the activities of spatially discrete populations of neurons. Such a discoordination could potentially disrupt the synchrony of oscillatory activity between connected neural populations,[49] which has long been proposed as a necessary requirement for the effective binding of sensory and arguably cognitive features.[50] However, in a more specific sense, it is possible that damage to the frontal fasciculi could cause conduction delays in frontally generated, posteriorly projecting neural signals, such as efference copies. Efference copies refer to neural signals, which often originate in the motor-initiation areas of the frontal lobe, that are "copies" of the motor plans associated with impending self-generated movements. These efference copies are thought to be transmitted or "fed forward" to sensory areas of the brain where they generate neural representations of the expected sensory consequences of the movement or corollary discharges.[51] (The terms "efference copy" and "corollary discharge" have been used somewhat inconsistently and often interchangeably in the neuroscience literature. In this article, we use efference copy to mean a copy of a motor command that is typically sent from motor-initiation areas to sensory regions. This efference copy is used to generate a neural representation of the expected sensory consequences of the impending action, which we refer to as a corollary discharge.) These corollary discharges are then compared with, or "subtracted from," the actual sensory input (ie, "sensory reafference") associated with executing the movement. When

the corollary discharge and sensory reafference are well matched, the subtractive comparison results in suppression or dampening of the sensory stimulation produced by self-generated movements.[52] While the primary functions of efference copies are thought to include preventing neural desensitization and undesired motor reflexes,[53] there is evidence to suggest that they also play a role in "tagging" self-generated actions as being self-generated, thereby enabling a distinction to be made between sensations resulting from self-generated movements and sensations resulting from changes in the external world.[53–55]

Feinberg[8] and Frith[9] first developed the idea that many of the most distinctive symptoms of schizophrenia—most notably the passivity experiences and certain types of auditory hallucinations—could be explained by efference copy/corollary discharge abnormalities disrupting patients' ability to distinguish between internally and externally generated events. Evidence for this theory has been provided by studies showing that patients with schizophrenia exhibit abnormally high levels of neural activity to self-generated sensory stimuli.[56–59] The theory presented here provides a potential explanation as to both how and why efference copies/corollary discharges might be abnormal in schizophrenia patients. Specifically, we suggest that structural abnormalities in the fasciculi connecting the motor-initiation areas of the frontal lobe with the temporal and parietal cortices cause conduction delays in the efference copies initiated by self-generated actions and arguably self-generated cognitions more generally.[8] These conduction delays result in the delayed generation of corollary discharge signals in sensory regions, which consequently occur "too late" to suppress the sensory activation associated with the self-generated actions. This, in turn, results in confusion as to the origins of these actions and hence passivity experiences in the case of willed motor actions and auditory hallucinations in the case of willed cognitions.[8,9] To reiterate, the idea is that confusions of agency arise when efference copies arrive at their neural destinations and generate corollary discharges asynchronously with the evoked activity they are intended to suppress. Consistent with this idea, Blakemore and colleagues[60] reported that while healthy participants rated self-generated tactile sensations as less ticklish than externally generated sensations when both were generated indirectly with a robotic arm, they rated the sensations as equally ticklish if a subsecond delay was imposed between when participants instructed the arm to tickle and when it actually executed the instruction. We suggest that the results of Blakemore and colleagues[60] were caused by participants' efference copies arriving at their somatosensory cortex "too early" to suppress the sensory activity evoked by the robotic arm, ie, because of the imposed delay. The basic idea that mistimed corollary discharges could underpin schizophrenia patients' abnormal perception of self-generated actions is also consistent with the suggestion of Arnfred and colleagues,[61] who argued that the increased latencies of early proprioception-evoked potentials exhibited by schizophrenia patients could best be explained by instabilities in the corollary discharge signals involved in preparing the sensory cortices for feedback.

If the passivity experiences and auditory hallucinations characteristic of schizophrenia result from dysmyelination-induced conduction delays in efference copies causing confusion as to the origins of self-generated actions and cognitions, then the question remains as to what causes the excessive dopamine neurotransmission that has been associated with schizophrenia and the psychotic symptoms in particular. As we discuss further below, we suggest that this excessive dopamine neurotransmission arises, at least in part, as a consequence of the same prediction errors that underpin the confusions of agency associated with the passivity experiences and auditory hallucinations.

The sensory consequences of self-generated actions are normally the most predictable and thus least salient of events, as they are typically estimated accurately from corollary discharges via a forward model.[51,52] We suggest that if dysmyelination-induced delays in the efference copies initiated by self-generated actions cause a discrepancy between the sensory feedback predicted by the forward model (ie, the corollary discharge) and the observed sensory feedback, then this represents a prediction error, which is both a phenomenologically and neurophysiologically salient event. On a phenomenological level, the perception of salience in a self-generated action could lead to confusion as to the origins of the action and hence, as discussed above, passivity experiences in the case of willed motor actions and auditory hallucinations in the case of willed cognitions. However, on a neurophysiological level, a prediction error of this nature could cause an increase in the phasic activity of midbrain dopaminergic neurons, given the role that these particular neurons are believed to play in signaling salience in general and prediction errors in particular.[62–65] An implication here, for which there is some evidence,[66] is that increases in the phasic activity of midbrain dopaminergic neurons will result in increased dopamine release at target sites, such as has been inferred to occur in patients with schizophrenia.[67,68] The increased activity of these dopaminergic neurons could in turn lead to the perception of salience in previously insignificant events, as per Kapur's[11] model of psychotic symptomatology. This could worsen the budding passivity experiences and auditory hallucinations and also cause previously insignificant events in the external world to be perceived as salient and of special significance to the patient, thereby causing other first-rank psychotic symptoms, such as delusions of reference. To reiterate, we suggest that while passivity symptoms and auditory hallucinations could, in some patients, initially arise because of dysmyelination-induced conduction delays in the efference copies initiated by willed thoughts and actions, the resultant increases in the phasic activity of midbrain dopaminergic neurons could amplify these

symptoms and concurrently trigger additional psychotic symptoms associated with schizophrenia. With respect to the etiology of negative symptoms, it is possible that the increased phasic activity of these dopaminergic neurons could "drown out" the dopaminergic activity typically associated with reinforcing or motivationally salient stimuli, as per the suggestion of Roiser et al.[69] The consequently reduced valence of typically reinforcing stimuli could underlie such negative symptoms of schizophrenia as anhedonia, avolition, and apathy.[70]

On a technical note, it should be acknowledged that prediction errors have not always been associated with increased firing rates in dopaminergic neurons. On the contrary, Schultz et al[62] used a reward-conditioning procedure and found that while "positive" prediction errors (ie, prediction errors for which the actual outcome was more rewarding than the predicted outcome) were associated with increased firing rates in dopaminergic neurons, "negative" prediction errors (ie, for which the actual outcome was less rewarding than the predicted outcome) were associated with decreased firing rates. It is not clear whether the prediction errors we hypothesize to occur in schizophrenia patients (ie, unexpectedly high levels of neural activity to self-generated actions and thoughts) are positive or negative in the aforementioned sense, and thus whether they would necessarily be expected to result in increased levels of phasic dopaminergic activity. However, it is possible that the positive/negative dichotomy is not relevant to these particular prediction errors, given that they are not obviously related to expectations of reward. On this point, it is interesting to note that dopaminergic neurons have also been found to "increase" their firing rates in response to unpredictable and salient stimuli that are not conditioned to reward.[63,64] This scenario may be more relevant to the prediction errors we hypothesize to occur in schizophrenia patients, given that it is not clear that these particular predictions (eg, regarding the sensory consequences of self-generated actions) necessarily relate to reward conditioning.

If the psychotic symptoms of schizophrenia are caused by conduction delays in efference copies that are, in turn, caused by abnormal myelination of the frontal white matter fasciculi, then the question remains as to why the relevant neural circuits do not adapt to this delay, given their demonstrable plasticity.[71] One possible answer is that the myelin abnormalities—and by implication the conduction delays—vary in magnitude over the course of the illness. Such a possibility would be akin to the cycles of demyelination and remyelination often experienced by patients with multiple sclerosis[72]: cycles that have been shown to be associated with fluctuations in conduction velocity[46] and symptomatology, including psychotic symptomatology.[73–75] A similar idea has previously been proposed by Garver and colleagues[76] who suggested that the patients in their study may have experienced "compromised myelin integrity during psychosis with repair during remission" (p. 49), given that they showed marked increases in mean diffusivity with Diffusion Tensor Imaging when floridly psychotic as opposed to when experiencing a medication-induced remission of psychotic symptoms. An alternative explanation for why schizophrenia patients might experience variable conduction delays in their corollary discharges is suggested by the results of Rasminsky and Sears.[77] Rasminsky and Sears[77] experimentally dysmyelinated the ventral roots of the spinal cord in rats and found that the conduction velocities of impulses traveling along these fibers were both slower and abnormally variable compared with impulses traveling along healthy fibers. Furthermore, the extent of the observed conduction delays were found to be dependent on the frequency of stimulation, with high frequency stimulation resulting in larger and more variable conduction delays than low frequency stimulation. If, as discussed previously, schizophrenia patients experience dysmyelination in their frontal fasciculi, then the consequently variable conduction velocities of corollary discharges traveling along these fasciculi could lead to variation in the extent to which they suppress their sensory targets. This, we suggest, could give rise to variability in the magnitude of the associated prediction errors, which could lead to variability in the activities of midbrain dopaminergic neurons, which could ultimately lead to the dynamic profile of psychotic symptoms often exhibited by patients with schizophrenia. Furthermore, given the role that spike-timing dependent plasticity has been proposed to play in efference copy circuits,[78] variable conduction delays might also lead to unpredictable variations in synaptic strength, such as have previously been suggested to underlie corollary discharge abnormalities in patients with schizophrenia.[78]

To summarize, we suggest that psychotic symptoms can arise via 2 distinct yet interconnected mechanisms. First, we suggest that myelin abnormalities cause conduction delays in corollary discharges, which in turn cause prediction errors during the performance of self-generated actions and thoughts. On a phenomenological level, these prediction errors cause confusion as the origins of these thoughts and actions and give rise to passivity experiences and auditory hallucinations. On a neurophysiological level, these prediction errors give rise to the second, more general cause of psychotic symptoms, namely the increased phasic activity of midbrain dopaminergic neurons. This hyperdopaminergia worsens the budding passivity experiences and auditory hallucinations and gives rise to new psychotic symptoms, such as delusions of reference. It is also worth noting that the basic idea that a perturbation of the dopamine system can lead to a vicious cycle of prediction errors and dopamine release is conceptually similar to the highly influential incentive salience model of addiction proposed by Robinson and Berridge[79] in which exposure to a drug causes modifications to the brain systems involved

in reward and makes them hypersensitive to the drug and drug-related stimuli. The fact that the dopamine system in particular is implicated in drug addiction suggests that this system may be especially prone to the development of such pathological resonances.

The theory presented here attempts to explain how 3 of the most distinctive features of schizophrenia—namely its periadolescent onset, its excessive dopamine neurotransmission, and its pathognomonic clinical symptoms—could all potentially arise from a single underlying cause. Specifically, the theory suggests that in schizophrenia patients, aberrant myelination of the frontal white matter fasciculi during periadolescent neurodevelopment causes irregularities in the timing of corollary discharges. The proposed theory is clearly highly speculative and would benefit from substantially more supporting evidence. To this end, the article will conclude with some empirical predictions of the theory which future studies may find worth investigating.

Prediction 1

Disrupting normal periadolescent myelination in vivo will cause an increase in the phasic activity of midbrain dopaminergic neurons and increased dopamine release in target areas. Indirect evidence for this prediction has been provided by Roy et al,[80] who disrupted normal oligodendrocyte development in mice by blocking the signaling of a necessary growth factor, Neuroregulin-1. In addition to the anticipated myelin abnormalities and conduction delays, the affected mice also showed significantly increased levels of dopamine receptors and transporters in the nucleus accumbens and striatum, similar to those exhibited by patients with schizophrenia.[68]

Prediction 2

If the passivity symptoms of schizophrenia are ultimately caused by delayed efference copies generating corollary discharges that are too late to suppress the sensory-evoked activity, then it should be possible to rectify the synchrony of the arriving signals by delaying sensory feedback by the duration of the conduction delay. Preliminary evidence for this prediction comes from a recent study by Whitford et al,[81] who found that while schizophrenia patients showed the characteristically subnormal levels of N1 suppression in the electroencephalogram to self-generated, button-press elicited auditory stimuli, these suppression abnormalities could be rectified by imposing a 50-ms delay between the willed action and the auditory stimulus.

Prediction 3

If the excessive dopamine neurotransmission typical of schizophrenia is, at least in part, a consequence of the prediction error associated with the erroneous perception of a self-generated action as externally generated, it should be possible to induce a phasic dopamine response in healthy individuals by experimentally manipulating their feelings of agency when performing a willed action. While this prediction is a fundamental tenet of the theory, the challenge will lie in accurately measuring in vivo changes in phasic dopamine, in real time, while participants perform an experimental task in which their feelings of agency are manipulated. While some recent studies have inferred changes in the activity of dopaminergic neurons on the basis of variations in the blood oxygen level–dependent signal in midbrain nuclei,[82,83] comprehensively testing this prediction may potentially require the development of new imaging technologies that are capable of measuring changes in phasic dopamine activity, in vivo, and in real time.

Prediction 4

It should be possible to identify a subset of schizophrenia patients who experience passivity experiences/auditory hallucinations as a result of conduction delays arising from abnormalities in frontal myelination, as opposed to from excessive dopamine neurotransmission per se. These patients would be expected to show residual levels of these symptoms even after treatment with dopamine antagonistic antipsychotic medications. Furthermore, these patients might also be expected to show more severe structural abnormalities in frontal fasciculi relative to patients who show no residual passivity experiences/hallucinations after antipsychotic treatment.

Prediction 5

Arguably the most clinically significant prediction of the theory is that if some cases of schizophrenia are ultimately underpinned by the abnormal myelination of frontally projecting fasciculi during periadolescent neurodevelopment, then it should be possible to use remyelinating medications, such as are currently used in the treatment of multiple sclerosis,[84] in the treatment of the disorder.[13] If the theory is correct, then these remyelinating medications would have a significant advantage over the current generation of antipsychotic drugs in that they would treat the fundamental cause of the symptoms in these patients (ie, the dysmyelination underlying the conduction delays in efference copies), as opposed to a secondary cause (ie, the excessive dopamine neurotransmission).

We would like to clarify 2 points regarding the theory. First, we do not mean to suggest that all patients diagnosed with schizophrenia, far less all patients diagnosed with psychosis, necessarily have abnormalities in either their white matter fasciculi or corollary discharge mechanisms. In keeping with the idea of dopamine dysfunction as the "final

common pathway" for the development of schizophrenia,[85] we suggest that many schizophrenia patients will not experience abnormalities in their white matter fasciculi but will instead experience various other brain abnormalities, so long as they ultimately result, either directly or indirectly, in dopamine dysfunction. For example, some schizophrenia patients may experience hyperdopaminergia as a result of abnormalities in the mechanisms of dopamine clearance. Such a mechanism, eg, may underlie the very high rates of schizophrenia (~25%) in patients with velocardiofacial syndrome, given that these patients are typically missing the COMT gene known to be involved in dopamine catabolism.[86] Second, although the current article has focused on the role of white matter pathology in the etiology of schizophrenia, it is important not to marginalize the role of gray matter pathology in the development of the disorder. There are now well over a 1000 neuroimaging and microscopic studies that have identified gray matter abnormalities in patients with schizophrenia—far more, it should be noted, than have observed white matter abnormalities.[22,24] It is likely that gray matter abnormalities play a causal role in the development of many, if not most, cases of schizophrenia. The relationship between the gray and white matter abnormalities observed in patients with schizophrenia is manifestly unclear. That is, it is not clear whether the gray matter abnormalities cause the white matter abnormalities, the white matter abnormalities cause the gray matter abnormalities, or the gray and white matter abnormalities arise from independent pathological processes.[87] This caveat aside, however, it is tempting to speculate that there may, in some patients, be a relationship between myelin abnormalities and gray matter atrophy. For example, there is evidence to suggest that one of the major factors influencing whether a synapse in the embryonic nervous system survives development is the synchrony of its activity relative to the activity of other synapses on the same neuron. Specifically, a synapse is more likely to be eliminated if it is asynchronously active relative to other synapses on the same neuron.[88] If similar mechanisms for synaptic elimination occur for the "synaptic prune" that normatively occurs during periadolescence and if dysmyelination results in disrupted neural synchrony in schizophrenia patients (as suggested in this article), then it is perhaps feasible that dysmyelination could result in the elimination of synapses that would otherwise have been preserved, ie, a period of "hyperpruning" in schizophrenia patients.[13,22,89,90] Such a reduction in the number of synapses and their associated infrastructure could potentially account for the gray matter atrophy typically observed in schizophrenia patients and would be consistent with the observation that patients with schizophrenia show an increase in neuron density but not a reduction in neuron number.[91]

While enormous strides have been made into understanding exactly what is abnormal in patients with schizophrenia—in terms of its neuroanatomical, neurophysiological, neurochemical, and neuropsychological underpinnings—less progress has been made in elucidating the underlying mechanisms of pathology. The theory presented here, in which schizophrenia is proposed to arise from a dysmyelination-induced desynchronization of the corollary discharges involved in distinguishing between self-generated and externally generated events, aims to provide some insight into the nature of these mechanisms. Regardless of the validity of this particular theory, it is clear that gaining a better understanding of the mechanisms underlying the myriad pathologies exhibited by patients with schizophrenia is necessary if we are to develop more rational and efficacious treatment strategies for this terrible disorder that causes so much suffering to so many people.

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